6 October 2000

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1-23
12420 Parklawn Drive
Rockville, MD 20857

7010 '00 OCT 12 A9:35

PETITION FOR RECONSIDERATION

Dear Sir or Madam:

I respectfully submit this petition for reconsideration of the decision of the Commissioner of Food and Drugs in Docket No. 99P-4053/CP1 regarding the proposed amendment to classification and product labeling for the sympathominetic amine phentermine.

A. Decision Involved

In a letter dated September 7, 2000, Janet Woodcock, M.D., Director of the Center for Drug Evaluation and Research at the Food and Drug Administration, denied the citizens petition referenced above. In that petition, we sought to amend the required product labeling and patient insert for the sympathominetic amine phentermine (in all its salt forms) to indicate that it inhibits the enzyme monoamine oxidase and thus should be classified as a monamine oxidase inhibitor.

B. Action Requested

Under the regulations at 21 CFR 10.33, the Commissioner may reconsider the decision in a citizens petition and amend a required product labeling. I respectfully request the Commissioner to nullify her earlier decision and modify the current language of the labeling and patient insert to read as follows:

> "Phentermine is capable of inhibiting monoamine oxidase (MAO) and therefore should not be used concurrently with sympathomimetic amines or selective serotonin reuptake inhibitors (SSRI)."

C. Statement of Grounds

The decision of the Commissioner was based on inaccurate scientific data. The relevant information and views contained in the supporting documentation included with the citizens petition clearly show that the Commissioner would have had sufficient justification to grant the request of the citizens petition. The specific grounds for reconsideration are as follows:

99P 4053

PRC 1

1. The letter denying the petition states on page three that the accepted manuscript from the *Journal of Biochemical Pharmacology* was not submitted for review. On December 16, 1999, I submitted five (5) copies each of both *Biochemical Pharmacology*'s letter to Dr. Richard J. Wurtman, informing him that his paper had been accepted for publication, and the article itself, copies of which were in the original citizens petition. I attach a copy of that letter with this petition for reconsideration.

2. The proper way to express inhibition by a reversible MAOI is by the Ki value. The proper way to express the inhibition by an irreversible inhibitor is by the EC-50. Granted one cannot make a direct comparison since the mechanisms of action are different, however both values represent the value at which 50% of the enzyme is inhibited. Also, the value for moclobemide is similar enough to that of phentermine to make a comparison that is meaningful.

   The letter denying the citizens petition states that a comparison between Ki and EC-50 cannot be made. However, in that same letter, Dr. Woodcock indicates that the concentration differences noted for phentermine and the irreversible agents mentioned (clorgyline, tranylcypromine) are "markedly higher." Quite clearly, a comparison is being made.

3. The fact that phentermine is "weak" at inhibiting MAO is irrelevant. The fact that it can inhibit the enzyme should be enough of a concern. FDA does not distinguish between weak and strong inhibitors in their approval of Patient Package Inserts, or any other literature.

4. The letter denying the citizens petition also cites a letter to *Synapse* from Dr. Richard Rothman ("Is Phentermine an Inhibitor of Monoamine Oxidase? A Critical Appraisal," *Synapse,* Vol. 32: 141-145, 1999). This letter was retracted by Dr. Rothman in a letter to the editor of *Synapse* (33:81, 1999) and was provided for review in the original citizens petition. I attach a copy of that letter for your review with this petition for reconsideration.

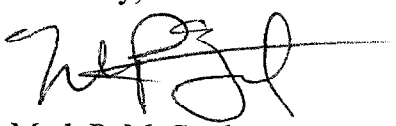
5. Maximum phentermine levels are reached from two to three hours following oral administration. They then drop off. The Douglas paper which is referred to by Rothman does not indicate the timing of dosing in relation to blood sampling. If the drug levels were administered the day before the sampling, then one would expect low levels.

6. Not all clinically useful MAOIs decrease 5-HIAA to the extent that the irreversible MAOIs do. Moclobemide has been reported to produce only a slight decrease (Holford et al) and this marker may not be that useful when investigating humans (Koulu et al 1989; Berlin et al, 1990).

By this petition for reconsideration and for the reasons given therein, I request the Commissioner to rescind the decision rendered in the citizens petition and to modify the

language of the labeling and patient insert in a manner that was outlined in this petition for reconsideration.

Sincerely,



Mark P. McGrath

Mark P. McGrath, Esq.

395 School Street
Watertown, MA 02472
(617) 923-7010

December 16, 1999

Mr. Lyle D. Jaffe
Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
5630 Fisher's Lane
Room 1061
Rockville, MD 20852

Dear Mr. Jaffe:

Per our conversation this morning, I am submitting the attached addenda in support of the Citizens Petition for the Proposed Amendment to Classification and Product Labeling for the Sympathominetic Amine Phentermine, FDA docket number 99P-4053/CP 1, originally filed on September 10, 1999.

The attachments consist of five (5) copies each of (a) Biochemical Pharmacology's letter to Dr. Richard J. Wurtman, informing him that his paper, "Characterization of Phentermine and Related Compounds as Monoamine Oxidase Inhibitors (MAOI)," authored by Ulus IH, Maher TJ and Wurtman RJ, has been accepted for publication; and (b) the article itself, copies of which were in our original citizens petition.

The article will appear in the next few months of Biochemical Pharmacology and is further evidence of scientific validation for this petition and for an affirmative decision by the FDA in this matter.

Please feel free to contact me if you need additional information or have any questions.

Sincerely,

Mark P. McGrath

Biochemical Pharmacology

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November 23, 1999

Dr. Richard J. Wurtman
Massachusetts Institute of
Technology
77 Massachusetts Ave., E25-604
Cambridge, MA 02139

Dear Dr. Wurtman:

Re: 252-3211-9-Revised-2, "Characterization of phentermine...," by I.H. Ulus et al.

Thank you for sending your revised manuscript to us. It is my pleasure to inform you that your paper is now acceptable for publication in *Biochemical Pharmacology.*

Proofs will be sent to you from Elsevier Science in New York in approximately three months. Please compare your edited manuscript and the galley proofs, checking carefully to see that they conform in every way and that there are no errors.

Enclosed please find a transfer of copyright agreement form for you to complete and return to us as soon as possible.

We look forward to the early publication of your manuscript.

Sincerely,

Robert H. Roth
Associate Editor

RHR:sed
Enclosure

ELSEVIER

Letter to the Editor

Retraction and Apology: Is Phentermine an Inhibitor of Monoamine Oxidase?

Dear Dr. Johnson:

My Letter to the Editor in the May 1999 issue of *Synapse* (32:141–145, 1999) raised questions as to the scientific basis for claims that phentermine acts as an inhibitor of monoamine oxidase at therapeutic doses, and was intended to provide a critical review of the phentermine/MAO hypothesis. In my introductory remarks, I asserted that an abstract co-authored by Richard Wurtman and his colleagues, ("phentermine, an unrecognized MAO inhibitor, probably increases free plasma serotonin when given with serotonin uptake blockers") "was widely publicized without the benefit of peer review, critical commentary, and sometimes without mention of important conflicts of interest." To the extent that statement may have misled any readers, I now retract it in its entirety, and offer my sincere apologies to Dr. Wurtman and to his colleagues, Dr. Timothy Maher and Dr. Ismail Ulus.

Specifically, I have learned that the abstract in question was in fact selected by the organizers of the International Congress on Obesity (8/29–9/3/98) as one of *a small number* of "hot topic" submissions worthy of special attention at the meeting, where open commentary on the research was invited, including a poster presentation by the three co-authors. The attention given their work at that venue, of which I was unaware, would indicate that their preliminary report received greater scientific scrutiny than is given to the typical meeting abstract in the biomedical sciences. Moreover, although my *Letter to the Editor* cited also a study by Maher, Ulus, and Wurtman published subsequently in the LANCET (Maher TJ, Ulus IH, Wurtman RJ. 1999. Phentermine and other monoamine oxidase inhibitors may increase plasma serotonin when given with fenfluramines. Lancet 353:38), the casual reader may not have inferred from my citation alone the distinction conferred on the latter report by virtue of its publication in the LANCET, an international journal that is known for its peer-reviewed content.

I now wish to clarify that with regard to my statement concerning "important conflicts of interest," my statement was not meant to imply that these authors personally had failed to disclose such information where it existed. Rather, my remark was meant as a comment on the reporting practices of news media that disseminated their findings from this area of scientific inquiry—some of which deemed it important to include mention of factual information regarding the various professional interests and affiliations of authors—and others of which did not. I am advised that Dr. Maher and his colleagues disclosed any possible conflicts of interest when their work was submitted for publication, and that as a matter of routine, such information was also included in press publicity material issued by the Massachusetts Institute of Technology and the Massachusetts College of Pharmacy and Health Sciences (http://web.mit.edu/newsoffice/nr/1998/fenphen.html; http://www.mcp.edu/news/1-4-99.htm). In some subsequent news reports, this information was published and in others not.

It is a matter of public record that I am Board Certified Psychiatrist and Medical Director of BE-LITE, a chain of for-profit weight-loss centers (www.belite.com), and that I use phentermine and a variety of other FDA-approved medications in the treatment of obesity and psychiatric disorders. The fact that I am Medical Director of BE-LITE was made known to *Synapse* but was not disclosed to readers of the Journal because it was not deemed to be relevant. I do not have any financial interests in any pharmaceutical companies, including ones which manufacture or sell phentermine.

Finally, to the extent that my comments noted in the first paragraph of this letter, or the omission of my affiliation misled any of the readers of *Synapse*, I offer my sincere apologies.

Sincerely,
Richard B. Rothman, M.D., Ph.D.

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